REMARKS/ARGUMENTS

With this amendment, claims 60, 66, and 81-83 are pending. Claims 62, 64 and 68 are withdrawn and claims 1-59, 61, 63, 65, 67, and 69-80 are cancelled. For convenience, the Examiner's rejections are addressed in the order presented in the October 19, 2004, Office Action.

I. Status of the claims

Claim 1 is amended to recite that the bacterial sialyltransferase is an α2,3-sialyltransferase. Support for this amendment is found throughout the specification, for example, at Table 4 on page 24. This amendment adds no new matter. Claim 1 is also amended to recite an isolated bacterial 2,3-sialyltransferase. Support for this amendment is found throughout the specification, for example, at page 6, lines 1-9 and at page 23, lines 11-12. This is not a limiting amendment and further, does not add new matter.

II. Sequence compliance

The Office Action requests that a sequence listing be filed to identify a sequence found on page 3 of the specification. Applicants have submitted a separate communication under 37 CFR §§1.821-1.825 with an amendment and a paper copy of the sequence listing. A computer readable sequence listing for the instant application is identical with the Sequence Listing submitted for Appln. No. 09/007,741, filed August 27, 1999, (this application's parent), and the Examiner is requested to please use the computer-readable form filed therein.

III. Rejections under 35 U.S.C. §112, second paragraph

Claims 60, and 81-83 are rejected are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, the Office Action alleges that the claims are indefinite for unmodified use of the phrase "bacterial sialyltransferase." To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

In order to expedite prosecution, claim 60 is now amended to recite "bacterial α2,3-sialyltransferase." Those of skill will recognize that the designation α2,3 refers to the linkage between a sialic acid molecule and a saccharide group. This linkage is formed by a subset of sialyltransferases designated as α2,3 sialyltransferases. In view of the above amendment and arguments, Applicants respectfully request withdrawal of the rejection.

IV. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 60, 65, and 81-83 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. According to the Office Action, the specification does not enable one of skill to make and/or use the invention commensurate in scope with the claims. The Office Action also alleges that undue experimentation is required to practice the claimed invention. In order to expedite prosecution, claim 65 is cancelled. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The Office Action indicates at pages 5-6 that the specification does enable a method of sialylating a saccharide group on a recombinant glycoprotein using an α2,3-sialyltransferase isolated from *C. jejuni*. Because of that statement, Applicants believe that, at a minimum, claim 66 is allowable.

The Office Action alleges that the specification does not enable use of bacterial α2,3-sialyltransferases in the claimed methods, and that such use is unpredictable and would require undue experimentation on the part of those of skill. First Applicants submit that the disclosure adequately teaches how to use bacterial sialyltransferases activities to sialylate a recombinant glycoprotein. Second, even if some bacterial sialyltransferase activities are not able to sialylated a recombinant glycoprotein, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. (*See*, *In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971)). In the present application, one of skill would know how to avoid inoperative embodiments and sialylate recombinant glycoproteins using the claimed methods with bacterial sialyltransferase activities without undue experimentation. Moreover, the present application provides guidance in the form of assays and working examples for sialylation of recombinant glycoproteins using bacterial sialyltransferase activities.

Assays for sialylation of recombinant glycoproteins by sialyltransferase activities, including bacterial sialyltransferase activities is disclosed at page 11, lines 24-31; page 13, line 30 through page 17, line 24; page 21, line 4-22; page 22, lines 18-24; page 23, line 2 through page 25, line 9. Exemplary recombinant glycoprotein substrates (α-1 acid glycoprotein (AGP) and other glycosylated proteins) for the reaction are disclosed at page 11, lines 26-30 and Table 5, page 25. AGP, for example, is commercially available from CalBiochem EMD Biosciences, Inc.

The Office Action appears to allege that the claims are not enabled because they allegedly encompass an "extremely large number of ST enzymes". Office Action at page 6. Applicants respectfully assert that only a few bacterial species make sialylated oligosaccharides and are known to provide sialyltransferase activity. Six of those species are disclosed in the specification: *Neisseria meningitides, Neisseria gonorrheae, Campylobacter jejuni, Haemophilus somnus, Haemophilus influenzae,* and *Photobacterium damsela. See, e.g.,* specification at page 24, Table 4. Thus, those of skill would know to limit bacterial sialyltransferase activities to bacteria that make sialylated oligosaccharides. In view of the handful of bacteria that have sialyltransferase activities, any experimentation required to practice the claimed methods would not be undue.

In view of the above amendments and arguments, Applicants respectfully request withdrawal of the rejection for alleged lack of enablement.

V. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 60, 66, and 81-83 are rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. According to the Office Action, the specification lacks description of the claimed invention, such that a skilled artisan would recognize that Applicants had possession of the claimed invention at the time of filing. The claims are directed to methods of sialylating saccharide groups on a recombinant glycoprotein, using an isolated bacterial α2,3-sialyltransferase activities. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

Applicants assert that at the time of filing the application, those of skill would have recognized that the inventors were in possession of the claimed invention. The specification describes methods of sialylating recombinant glycoproteins enzymatically, using sialyltransferase activities. As part of the description of the methods, the specification provides description of the components of the sialylation reaction mixtures, including sialyltransferase activities. The rejection appears to focus only on the description of the enzymes that provide the sialyltransferase activities and not on the other reaction components or the steps of the method. At the time of filing, a number of organisms were known to have sialyltransferase activities, including a subset of bacterial species. However, as bacteria lacked glycoproteins, bacteria were not recognized by those of skill to provide sialyltransferase activity toward glycoprotein substrates. The specification at page 9, lines 12-22 briefly describes the status of bacterial glycosyltransferases at the time of filing. The inventors provided the first disclosure of a bacterial sialyltransferase activity that could be used to sialylate glycoproteins with the filing of the priority application. For the methods of the amended claims, the bacterial sialyltransferase activity is provided by an isolated bacterial sialyltransferase, *i.e.*, an enzyme that is "at least about 80% pure." Specification at page 6, lines 1-9. Isolated bacterial sialyltransferases include proteins isolated from their species of origin without genetic modification or proteins that have been isolated after recombinant production. Once bacterial glycoprotein sialyltransferase activities were discovered, those of skill would have recognized that the activity providing sialylation of glycoproteins was not restricted to a particular bacterial sialyltransferase and that the inventors were in possession of the claimed invention.

The invention provides ample disclosure of the steps required to sialylate a recombinant glycoprotein using a bacterial sialyltransferase, *i.e.*, the claimed methods. The steps of the claimed methods are straightforward: contact a recombinant glycoprotein that comprises a galactose or N-acetylgalactosamine acceptor moiety and a sialic acid donor moiety with an isolated bacterial α2,3-sialyltransferase in a reaction mixture that provides reactants required for activity. The contact occurs for sufficient time and under appropriate conditions to allow transfer of sialic acid from the donor to the acceptor saccharide. The steps are described in the specification. Assays for sialylation of recombinant glycoproteins by sialyltransferase activities,

including bacterial sialyltransferase activities, *i.e.*, the claimed methods, are disclosed at page 11, lines 24-31; page 13, line 30 through page 17, line 24; page 21, line 4-22; page 22, lines 18-24; page 23, line 2 through page 25, line 9. Exemplary recombinant glycoprotein substrates (α-1 acid glycoprotein (AGP) and other glycosylated proteins) for the reaction are disclosed at page 11, lines 26-30 and Table 5, page 25. Results of experiments to sialylate recombinant glycoproteins using bacterial sialyltransferase activities are disclosed at page 22, lines 18-24. After review of this disclosure, one of skill in the art would recognize that the inventors were in possession of all of the methods necessary to practice the invention.

In addition, the USPTO's Synopsis of Application of Written Description Guidelines acknowledges that when a process is claimed and the novelty of the process is in the method steps, description of particular nucleic acids used in the method is not required. Applicants direct the Examiner's attention to Example 18 of the Synopsis of Application of Written Description Guidelines which analyzes a claim directed to a method of producing a protein of interest in *Neurospora* mitochondria by transforming the mitochondria with a nucleic acid that encodes the protein of interest. No specific nucleic acid or amino acid sequence is found in the claim. In these Guidelines, the Patent Office concluded that the claim was adequately described within the meaning of 35 U.S.C. §112, first paragraph. In particular, note the Patent Office's rationale:

> A review of the specification reveals that *Neurospora crassa* mitochondrial gene expression is essential to the function/operation of the claimed invention. A particular nucleic acid is not essential to the claimed invention.
>
> A search of the prior art reveals that the claimed method of expression in *Neurospora crassa* is novel and unobvious. The claim is drawn to a genus, *i.e.*, any of a variety of methods that can be used for expressing protein in the mitochondria.
>
> There is actual reduction to practice of a single embodiment, *i.e.*, the expression of β-galactosidase.
>
> The art indicates that there is no substantial variation within the genus because there are a limited number of ways to practice the process steps of the claimed invention.
>
> The single embodiment is representative of the genus based on the disclosure of *Neurospora crassa* mitochondria as a gene expression system, considered along with the level of skill and knowledge in the gene

expression art. One of skill in the art would recognize that applicant was in possession of all of the various expression methods necessary to practice the claimed invention.

Conclusion:

The claimed invention is adequately described.

Therefore, the present claims are described and Applicants respectfully request withdrawal of the rejection for alleged lack of written description.

VI. Rejections for obviousness-type double patenting

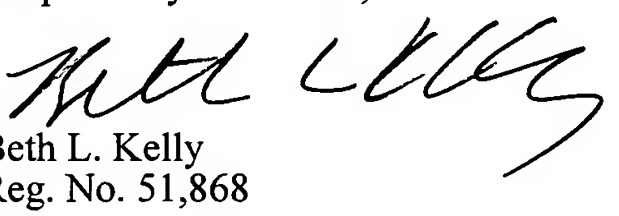
In response to the obviousness-type double patenting rejection over claims in the parent patent (US Patent 6,399,336), Applicants will file an appropriate terminal disclaimer, once the outstanding rejections are resolved.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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